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Medical Progress

The Relationship Between Genetics and Environment in the Pathogenesis of Rheumatic Diseases

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Major developments have taken place to further our understanding of the relationship between genetics and the environment in the pathogenesis of rheumatic disorders. The association between HLA markers and human disease is becoming clearer. For instance, HLA-DRW4 frequently occurs in patients with rheumatoid disease, and penicillamine and gold toxicity are seen most often in patients with HLA-DRW2 or DRW3. Antisera to B alloantigens help define the genetic differences between systemic lupus erythematosus and rheumatoid arthritis. As yet, the most dramatic link is that between HLA-B27 and primary ankylosing spondylitis. This same antigen is related, to varying degrees, with other members of the seronegative spondylarthritides and there is strong evidence that this association is related to HLA-B27, itself, rather than an associated disease gene. *Nevertheless, some data refute a single gene theory. We are just beginning to learn more about interactions between different genes on the sixth chromosome and genes on other chromosomes.*

The sex ratio of the spondylarthritides is now better defined. Sacroiliitis may have a comparable sex distribution although females have more peripheral joint disease and males have greater spinal involvement. Unfortunately, the explanation for these differences remains elusive.

The specific infective agents related to the development of rheumatic disorders are becoming clarified. Chlamydia, Salmonella, Yersinia and Shigella flexneri types 1b and 2a are arthritogenic, while Shigella sonnei appears not to cause disease. Although the Reiter syndrome is now considered a chronic disease, the reason for remissions and relapses remains unclear.

CHRONIC DISEASE often results from an interaction between the host and the environment. In the study of rheumatic disorders, geneticists and, in particular, immunogeneticists have made important strides in understanding host characteristics. At the same time, epidemiologists have begun to elucidate certain environmental factors. This review analyzes the relationship between genetics and the environment in the pathogenesis of rheumatic diseases.

Until recently, progress in rheumatology had

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been hampered by a lack of precise diagnostic definitions. Although we still suffer from ill-defined syndromes such as *seronegative rheumatoid arthritis* and the many forms of *degenerative joint disease,* there have been important developments in defining some seronegative arthritides in adults[1] and in children.[2]

Nurture and Nature

The relative contribution of nurture and nature varies for different rheumatologic conditions. For example, traumatic arthropathy can be considered entirely environmental in origin. In contrast, the Marfan syndrome is an autosomal dominant disorder with no environmental contribution. Most rheumatic conditions involve environmental and genetic factors in varying proportions. For example, the Reiter* syndrome may occur, preferentially, in patients with HLA (human leukocyte antigen)-B27, especially if these persons come into contact with a specific infective agent such as Shigella flexneri type 2a.

Certain disorders such as rheumatoid arthritis appear to be associated with specific HLA-DR antigens and, presumably, require unrecognized infective or other precipitating agents. Ill-defined diagnostic categories such as degenerative joint disease include numerous subsets which vary in their degree of genetic contribution and influence. For example, Heberden nodes, generalized postmenopausal osteoarthrosis and erosive osteoarthropathy are genetically related subsets, while degenerative disease of the first carpal metacarpal joint is predominantly determined by environmental factors. This review does not include heritable connective tissue disorders such as the Ehlers-Danlos syndrome (autosomal dominant) or arthropathies associated with autosomal recessive disease (for example, Wilson disease), X-linked recessive disorders (for example, hemophilia) or rare rheumatologic syndromes such as nail patella disease, a disorder that runs in families and is linked to one of the common blood groups (A, B or O).

Epidemiologic Studies

In general, the relationship between genetics and the environment in the pathogenesis of rheumatic diseases is evaluated by prevalence, racial, family and twin studies, together with analyses of age and sex distribution. In the past, analysis of blood group was of some help; now we can study HLA status and other genetic factors in patients with different rheumatic disorders.

TABLE 1.—*Explanation for Lack of Good Epidemiological Data on the Reiter Syndrome*

- No absolute diagnostic test
- Young adults: mobile community
- Venereal history suppressed
- Enteric features forgotten
- Clinically inapparent diagnostic features:
  - Silent mouth ulcers
  - Silent balanitis
  - Silent urethritis
- Nonspecific but clinically significant:
  - Eye disease
  - Skin disease
- Asymptomatic urethritis in females
- Asymptomatic cervicitis
- Misdiagnosis: seronegative rheumatoid arthritis
- Overlap between seronegative spondylarthritides (For example, the Reiter syndrome now considered ankylosing spondylitis)
- Fragmented care (a multisystem disorder)

In certain well-defined conditions, such as seropositive rheumatoid arthritis, epidemiologic studies are relatively simple to carry out. This disease is readily recognized in both sexes and its chronicity permits long-term studies. In contrast, prevalence and sex distribution data for the Reiter syndrome are virtually impossible to establish; some of the reasons for this difficulty are summarized in Table 1. There is no absolute diagnostic test, and reliance on long-term follow-up is hampered by the fact that the disease occurs in young adults who, by the nature of the disorder, form a mobile community. Not surprisingly, the important venereal history may be suppressed and possible enteric features forgotten. Such classic features as silent mouth ulcers and clinically inapparent balanitis may not be noticed by patient or physician, or may be self-limiting and no longer present when a patient's condition is evaluated. Nonspecific, though important, clinical features such as conjunctivitis, uveitis and keratodermia blennorrhagica may be mistaken for insignificant eye irritation or dermatitis. Moreover, many of these disease manifestations may antedate the arthropathy by months or years, sometimes clearing by the time the arthritic component develops. In women, the problem in diagnosis is compounded by the fact that urethritis and cervicitis are often clinically silent and frequently nonspecific.

For too long clinicians have relied on a catch-

*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

all diagnostic label, *seronegative rheumatoid arthritis,* for all nonspecific chronic inflammatory seronegative arthropathies. This term almost certainly includes many patients with ankylosing spondylitis, the Reiter syndrome and psoriatic arthropathy, the overlap between these entities further complicating the clinical features. Finally, many patients with the Reiter syndrome present to ophthalmologists, orthopedic surgeons, genitourinary specialists and others before an appropriate diagnosis is reached by a rheumatologist or other physician interested in the disease. Clearly, epidemiologic studies of the Reiter syndrome remain in their infancy because of a relative lack of clinical sophistication.

Prevalence Studies

Genetic as opposed to environmental influences can be studied by comparing the prevalence of a given disease within a population at large with that of first-degree relatives and nonconsanguinous household contacts. For example, the prevalence of gout is about 0.3 percent in a random white population, but rises to 6 percent in first-degree relatives of persons with the disorder.[3] Comparable figures for psoriatic arthropathy are about 0.1 percent and 5 percent, respectively.[4] Increased prevalence of ankylosing spondylitis among first-degree and second-degree relatives has long been recognized,[5] and the advent of HLA typing has clarified some, but not all, of these findings.

Sex Distribution

The sex ratio in rheumatic diseases is well defined in some disorders such as the Sjögren syndrome (9 females:1 male) and systemic lupus erythematosus (8 females:1 male), but is less clear in the B27-related disorders (Table 2). These sex differences may depend on hormonal modification, anatomy, the presence of the H-Y antigen[6] or other, as yet unidentified, sex-related factors.

Systemic Lupus Erythematosus: An Example

In contrast to psoriatic arthropathy or ankylosing spondylitis, disorders such as systemic lupus erythematosus have a plethora of serologic markers which make both genetic and environmental studies possible.[7] Evidence of environmental influences in the pathogenesis of systemic lupus includes the presence of anti-DNA antibodies in laboratory workers, antilymphocytic antibodies in spouses of patients, and immunoglobulin and complement deposition in skin biopsy specimens from spouses. Moreover, certain subsets of lupus are clearly drug related, procaine amide-induced lupus being the most easily recognized example. That homozygotic twins may be discordant for systemic lupus also attests to the essential influence of environmental factors.[7]

TABLE 2.—*Sex Ratios in Rheumatic Diseases**

Disease	*Females:Males*
The Sjögren syndrome	9:1
Systemic lupus erythematosus	
In persons under 15 years old	3:1
In persons 15 to 30 years old	9:1
In persons over 50 years old	2:1
Rheumatoid arthritis	3:1
Polymyositis	3:1
Polymyalgia rheumatica	2:1
Scleroderma	3:2
Polyarteritis nodosa	1:2
Gout	1:10
Pseudogout	1:1
Ankylosing spondylitis:	
Severe spinal disease	1:5
Clinical ankylosing spondylitis	1:3
Sacroiliitis	1:1
Sacroiliitis and peripheral arthropathy†	2:1
The Reiter syndrome:	
Nonspecific urethritis	1:5
Postvenereal Reiter syndrome	1:10
Shigellosis	1:1
Post-Shigella Reiter syndrome	1:1
Yersinosis	1:1
Yersinia arthropathy	1:1
Yersinia arthropathy and erythema nodosum	10:1

*Differences related to hormones, anatomy, the H-Y antigen or other factors.

†Dequeker J, Decock T, Walravens M, et al: A systematic survey of the HLA B27 prevalence in inflammatory rheumatic diseases. J Rheumatol 5:452-459, 1978.

An association of hormonal factors with lupus is suggested by the strong preponderance of females with this disease, as well as by the apparent increase in prevalence among male patients with the Klinefelter syndrome (XXY chromosome abnormality). Of note, the strong preponderance of females with lupus is not found among children and persons over 50 years of age. Laboratory studies showing hormonal modulation of the autoimmune disease in New Zealand mice offer further evidence of a hormonal effect.[8]

The role of genetic influences is also evident in the findings of racial and other studies. Systemic lupus erythematosus develops three times more frequently in blacks than in whites.[7] The

prevalence of lupus in a random population is about 1:1,000 to 1:10,000. In contrast, this disease develops in 1 percent to 2 percent of first-degree relatives.[7] Concordance among dizygotic twins provides similar figures,[7] while concordance for lupus among monozygotic twins occurs in 60 percent of the persons studied. Moreover, the prevalence of antinuclear factor (about 70 percent) and hypergammaglobulinanemia (85 percent) in monozygotic twins is evidence of the genetic contribution.[7] Recently, studies of HLA have suggested a link between lupus and HLA-B8 in whites and HLA-BW15 in blacks, and more specifically with HLA-DRW2 and DRW3 (relative risk of 3.7 and 3.0, respectively). Of major interest has been the description of a serum (Ia715) that was identified in 76 percent of lupus patients compared with 14 percent of controls (a relative risk of 19).[9] The link between C2 deficiency and lupus is well known[10] as is the association between slow acetylator status and drug-induced lupus.[11] The gene coding for C2 is found on the sixth chromosome, near the HLA-DR region, a finding that may explain the association between C2 deficiency and lupus.

The Histocompatibility Antigen System

The HLA gene-complex region of the sixth chromosome in humans is shown in Figure 1, and examples of disease associations are listed below each locus. The more important associations are with the HLA-B, D and DR loci. The HLA-A, B, C and DR antigens are coded for by four genes in the HLA region. The A, B and C antigens can be shown to be present by complement-mediated lymphocytotoxicity on peripheral blood lymphocytes and DR antigens shown on B lymphocytes derived from bone marrow.[12] The term DR (D related) replaces the older Ia nomenclature (immune associated). The HLA-A, B and C antigens are glycoproteins occurring on the surface of cells which consist of a light chain (molecular weight 12,000), a $\beta 2$ microglobulin, which is coded for by a gene on chromosome 15, and a heavy chain (molecular weight 43,000) which bears the antigenic terminal that confers HLA specificity on the molecule and is a product of the HLA-A, B and C loci. The HLA-DRW (W = workshop) antigens are also composed of dissimilar polypeptides, one with a molecular weight of 33,000 and the other of 28,000. The biologic relevance of the HLA-DR alloantigen system remains unclear. By extrapolating data from studies in mice, it may be that the antigens are associated with immune response genes. The DRW antigens are coded for by the HLA-D(R) locus which is either identical to or very closely related to the HLA-D locus that determines the lymphocyte-defined (by mixed lymphocyte culture) HLA-D antigens. To date, 20 HLA-A specificities have been identified, as have been 33 B, 6 C, 11 D and 7 DR alleles. Some of the A and B antigens, and all of the C, D and DR antigens are designated with the letter *W* followed by their appropriate number. For example, rheumatoid arthritis is associated with DW4 and DRW4. In the future, if the monospecific nature of the antigen is agreed upon, the suffix *W* will be dropped, as has already happened with HLA-B(W)27.

The functions controlled by genes in the HLA region have recently been reviewed.[12,13] They include the specificities mentioned above, as well as development of complement components, cell-cell recognition and possibly other activities. The classic *autoimmune* disorders such as myasthenia gravis, chronic active hepatitis, Addison disease, thyrotoxicosis and insulin-dependent diabetes

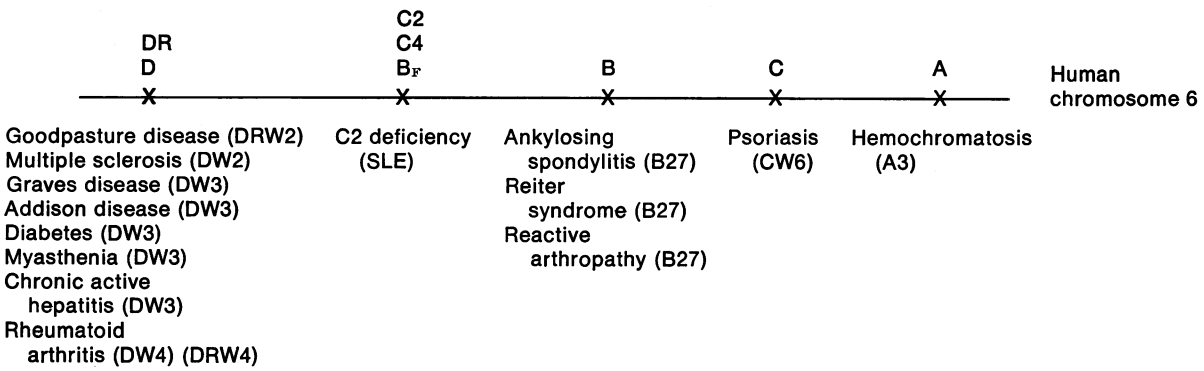

Figure 1.—HLA gene-complex region of human chromosome 6 with examples of disease associations listed below each locus.

mellitus are HLA-B8 associated. These diseases all have the propensity to develop autoantibodies directed at self (or intrinsic) antigens. In contrast, HLA-B8 is also linked with disorders such as gluten-sensitive enteropathy and enhanced graft rejection, conditions associated with antibodies directed toward extrinsic antigens.[12] Therefore, there is evidence for an HLA-linked gene responsible for nonspecific increase of antigens in immune responsiveness. Clearly, disease specificity must reside in other HLA or non-HLA-linked genes or result from poorly recognized environmental influences.

There is some evidence that persons with HLA-B8 are high responders. For example, those with HLA-B8 tend to have rapid clearance of hepatitis B surface antigen (HBsAg) and high-titer antibodies to rubella, measles, muscle and nuclear antigens in conditions such as hepatitis, and anti-insulin and antipancreatic cell antibodies in diabetes.[14] Furthermore, B8-positive patients with coeliac disease have higher frequencies of antibodies to gluten than do their B8-negative counterparts. In contrast, persons with HLA-B7 are low responders. Patients with thyrotoxicosis who are B7 positive tend to have low titers of antithyroid globulin and antimicrosome antibody, and B7-positive patients with insulin-dependent diabetes have low-titer anti-insulin antibodies.[12] Further, it has been suggested that there may be a protective effect of HLA-B7 in diabetes and coeliac disease. The effect of HLA-B8 (in linkage disequilibrium with DRW3) acting as a *high-risk* gene in conjunction with HLA-B15, in contrast to HLA-B7 (in linkage disequilibrium with DRW2) acting as a *low-risk* gene in the pathogenesis of juvenile diabetes mellitus[15] will be discussed below.

The Genetics of Rheumatoid Arthritis

Clinical Background

Is rheumatoid arthritis a single disease or a spectrum of unrelated disorders? Only during the last decade have the seronegative spondylarthritides been clearly distinguished from seropositive rheumatoid arthritis.[1] Indeed, these disorders (with ankylosing spondylitis as the prototype) may be differentiated from rheumatoid disease on historical, epidemiologic, geographic, ethnic, sex, age, clinical, pathologic, radiologic, immunologic, immunogenetic, serologic and even therapeutic grounds.[16] But what of seronegative rheumatoid arthritis? Clearly, in some patients, diseases given this diagnostic label (especially in those patients seen early in the course of their illnesses), will become seropositive later. Those with occult psoriasis (scalp, gluteal fold and periumbilical region) or sacroiliitis should be considered as having a seronegative spondylarthropathy (psoriatic arthropathy or ankylosing spondylitis). Persons in whom psoriasis develops later may have *psoriatic arthritis sine psoriasis*. This concept is useful for patients with an asymmetric arthropathy, dactylitis or, perhaps, family history of psoriasis.

The difficulty in recognizing the Reiter syndrome has been discussed. The onset of arthropathy in childhood probably involves a different disease process than for the adult seronegative disease. Certainly, it is just as naive to consider all seronegative rheumatoid arthritis a single disease as it is to lump together all arthritic disorders occurring in children as *juvenile rheumatoid arthritis*. We now recognize that the latter group of disorders falls into several well-defined subsets. It is probable that the same clarification will occur for this spectrum of diseases as with those occurring in adults. We should consider that patients have a *seronegative inflammatory polyarthropathy of unknown classification* rather than use the unrealistic and emotive term seronegative rheumatoid arthritis. In the interim, we cannot expect successfully to identify clear-cut genetic and environmental influences if we lump all of these diseases together as seronegative rheumatoid arthritis.

Despite the absence of environmental clues we have some tantalizing genetic findings regarding seropositive disease. It is generally considered that the prevalence of rheumatoid arthritis is about 1 percent;[17] in contrast, the prevalence among first-degree relatives is between 3 percent and 8 percent.[18] For decades, patients have told us that their rheumatoid arthritis "runs in families."

Immunogenetics

An initial search for a relationship between HLA-A, B and C antigens failed to show a link between the HLA region of chromosome 6 and rheumatoid disease. More recently, however, an association between HLA-D (and DR antigens) and rheumatoid arthritis has been determined.[19-22] This association was considered unique because no previous disorder had been linked to the D locus in the absence of any A, B or C association;

now another rheumatologic disorder, Goodpasture disease, has been linked with HLA-DRW2 in the absence of other HLA associations.

Initially, Stastny showed an association between HLA-DW4 and rheumatoid arthritis.[19] Of the patients in the study, 59 percent were DW4 positive while only 16 percent of the controls were positive. Later, McMichael and colleagues showed a similar link; their figures were 36 percent and 13 percent, respectively.[20] Thereafter, an association with DRW4 was found.[21,22] Of the patients, 70 percent were DRW4 positive in contrast to 28 percent of controls. Of interest, the DW4 relationship was found only in whites; only 14 percent of American blacks and 10 percent of Mexican-Americans with rheumatoid arthritis were DW4 positive,[19] indicating the need to study this association within different ethnic groups. A similar difference will be noted in the discussion on ankylosing spondylitis and the other spondylarthritides.

More recently, results of a study in London showed the presence of DRW4 in 34 percent of controls and in 56 percent of patients with rheumatoid disease.[22] Allowing for appropriate statistical corrections, there was a decrease in prevalence of DRW2 within the patient population; only 14 percent of the subjects were positive in contrast to 30 percent of controls. Furthermore, patients with rheumatoid arthritis and DRW2 were considered to have milder disease with lower titers of rheumatoid factor. The prevalence of nodules was also less. Therefore, DRW2 appears to protect persons from developing rheumatoid arthritis, but if the disease does occur it is less severe. DRW2 is in linkage disequilibrium with HLA-B7. As discussed earlier, HLA-B7-positive patients with autoimmune disorders tend to have low-titer antibodies to both intrinsic and extrinsic antigens.[12] Moreover, the protection of HLA-B7 and DRW2 has been discussed in relationship to insulin dependent diabetes.

In the same London study,[22] the findings showed that HLA-DRW3 was present in 30 percent of patients with rheumatoid arthritis and 27 percent of controls, a comparable distribution. However, patients with DRW3 tended to have stronger rheumatoid-factor seropositivity. This finding is correlated with the association between DRW3 (and HLA-B8, in linkage disequilibrium) and autoimmune disorders with enhanced autoantibody activity. For example, patients with chronic active hepatitis and HLA-B8 have higher antinuclear and antismooth muscle antibody titers than their B8-negative counterparts.[14]

Of particular interest was the suggestion that toxic reactions to gold and penicillamine occurred more frequently in rheumatoid arthritis patients with HLA-DRW2 or DRW3 compared with patients with other DRW antigens. Although these subsets were small and appropriate statistical corrections were not made, the possibility that drug toxicity may be genetically determined does not seem unreasonable. In some cases drug toxicity may be immunologically determined and an HLA-linked immune response mechanism appears possible. In general, it is recognized that penicillamine is relatively nontoxic in patients with Wilson disease when compared with those with rheumatoid arthritis. Moreover, penicillamine is administered in higher doses to patients with the former disease. Likewise, levamisole has been used for many years as an antihelmintic agent and was considered relatively nontoxic in these infective disorders. Now, bone marrow toxicity is seen relatively frequently in patients with rheumatoid arthritis, suggesting that certain host characteristics influence the degree of toxicity. Some investigators have suggested that levamisole is particularly toxic in HLA-B27-positive patients with rheumatoid arthritis. They have recommended that patients with this disease should be HLA typed before levamisole is given.[23] The suggestion that drug-induced systemic lupus is more apt to develop in patients who are slow acetylators than in their fast acetylator counterparts[11] was discussed above. No doubt HLA and non-HLA-linked genetic mechanisms that apparently influence drug tolerance should be studied further.

The Genetics of the Seronegative Spondylarthritides

Clinical Background

Spondylarthropathies should not be considered *rheumatoid variants*. The term is derived from the fact that these seronegative arthropathies have both spinal and peripheral joint involvement. The group includes the prototype, ankylosing spondylitis, as well as the Reiter syndrome, the spondylitic syndrome associated with inflammatory bowel disease, certain subsets of juvenile chronic polyarthropathy, the reactive arthritides (Salmonella, Yersinia and Shigella), psoriatic arthropathy and, possibly, Whipple disease and the Beh-

TABLE 3.—*Distribution of HLA-B27 in Different Healthy Populations*

Population	*Percent*
Aborigines	<1
Japanese	<1
Blacks:	
Africa	<1
United States	4
Whites:	
Great Britain	6-8
Scandinavia	10-14
North American Indians:	
Pima	18
Haida	50

cet syndrome. These conditions are interrelated at personal and familial levels. For example, sacroiliitis may develop in patients with inflammatory bowel disease or the Reiter syndrome and uveitis or spondylitis may develop in persons with psoriatic or Yersinia arthropathy. Moreover, patients with the Reiter syndrome are more likely to have relatives with psoriatic arthropathy or ankylosing spondylitis than would be expected to occur by chance alone; this increased prevalence of spondylitis among family members of probands with any of the spondylarthritides has been well recognized.

Immunogenetics

No HLA association is as close as that between HLA-B27 and the spondylarthropathies. Since 1973, when two groups of investigators described the link between HLA-B27 and ankylosing spondylitis,[24,25] there have been numerous articles published in which the association between HLA antigens and the group of related disorders that form the seronegative spondylarthritides has been analyzed. The distribution of HLA-B27 in different healthy populations is summarized in Table 3 and the frequency of the antigen in different rheumatic diseases is given in Table 4.

It has long been recognized that ankylosing spondylitis is more frequently seen in whites than in certain other races. For example, the disease is unknown in African blacks, very rare in Asians and seen less frequently in American blacks than whites.[26,27] These different ethnic prevalences are now recognized to follow the distribution of HLA-B27 in the normal population. For instance, HLA-B27 is present in less than 1 percent of Japanese[28] and African blacks, in 3 percent to 4 percent of blacks in the United States[29] (the difference due, in part, to racial admixture) and in 6 percent to 14 percent of whites. The highest known prevalence of B27 is in the Haida Indians[30] of British Columbia. About half the males tested are B27 positive and about 20 percent of these have sacroiliitis.

TABLE 4.—*HLA-B27 and Rheumatic Disease**

Disease	*Percent HLA-B27 Positive*
Ankylosing spondylitis†	90-100
Endemic Reiter syndrome‡	70-90
Psoriasis	5-10
Psoriatic arthropathy without sacroiliiitis	18-22
Psoriatic arthropathy with sacroiliitis	50-60
Seropositive juvenile rheumatoid arthritis	7-10
Juvenile chronic polyarthropathy without sacroiliitis	15-25
Juvenile chronic polyarthropathy with sacroiliitis	40-60
Inflammatory bowel disease	5-10
Inflammatory bowel disease with peripheral arthropathy	5-10
Inflammatory bowel disease with sacroiliitis	50-70
Yersinia infection	5-10
Yersinia-reactive arthropathy	80
Salmonellosis	5-10
Salmonella-reactive arthropathy	80-90
Shigellosis	5-10
Post-Shigella arthropathy (epidemic Reiter syndrome)	80
Uveitis	40-50
Chronic balanitis	90
Rubella arthritis	5-10

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†Japanese and blacks: 60 percent; Pima Indians, males: 50 percent; females: 10 percent.

‡Blacks: 60 percent.

Psoriasis, inflammatory bowel disease, yersinosis, shigellosis and salmonellosis are not B27 associated.[31] The prevalence of B27 in these disorders reflects that in the general population. However, as seen in Table 4, the arthropathies associated with the infections mentioned above are B27 associated, as are spinal manifestations of inflammatory bowel disease, psoriatic arthropathy and juvenile chronic polyarthropathy.[27] Some studies have suggested an increased prevalence of HLA-B27 in the last two disorders even in the absence of sacroiliitis. Of interest, HLA-B27 has been found present in only half of patients with psoriatic arthropathy or inflammatory bowel disease complicated by sacroiliitis. It seems, therefore, that the genetic influence of HLA-B27 is less necessary in the presence of psoriasis or in-

flammatory bowel disease. Conceivably, other genetic or environmental processes are also interacting with these primary disorders.

Apart from male Haida Indians, the association between HLA-B27 and ankylosing spondylitis is weaker in nonwhite populations. Only about 66 percent of Japanese[28] and 50 percent of American blacks[29] with the disease are HLA-B27 positive. The reason for this varying association may be related to the fact that B27, itself, is not the disease gene, but rather a marker for a specific disease-associated gene that is in varying linkage disequilibrium with B27 in different ethnic groups.

Our studies of the Pima Indians[32] have posed a further problem. HLA-B27 is present in 18 percent of healthy Pima Indians but in 57 percent of males with sacroiliitis. In contrast, the prevalence of B27 among female Pima Indians with sacroiliitis is only 10 percent. Overall, the prevalence of sacroiliitis is striking in both sexes; 15 percent of male and 24 percent of female Pima Indians have sacroiliitis. As is true in whites, uveitis occurs predominantly in those with sacroiliitis. The apparent lack of association between HLA-B27 and sacroiliitis in female Pima Indians cannot be explained.

The clinical situation is further complicated by the fact that different *formes frustes* of seronegative spondylarthritides are associated in varying degrees with B27. For example, balanitis alone[33] may be B27 related and reports of dactylitis, uveitis, calcaneodynia, seronegative oligoarthropathy and even shoulder capsulitis occurring in B27-positive subjects have appeared.[34] Other studies are needed to confirm these associations. Meanwhile, it remains uncertain as to why and how such disparate conditions can occur in one person—that is, in a single genetic situation. We followed up four patients with balanitis, all with HLA-B27, for two or three years before a classic picture of Reiter disease developed. These B27-associated *formes frustes* remind us that our diagnostic classification of these cases is often empirical, and we sometimes lump together or divide them incorrectly. Nevertheless, HLA-B27 has helped in understanding nosologic clustering on the one hand (ankylosing spondylitis, the Reiter syndrome, juvenile ankylosing spondylitis and psoriatic spondylitis) and subdivision or subsetting on the other (for instance, juvenile rheumatoid arthritis consists of various subsets, one of which being B27-related oligoarthropathy).

The effect of gene dosage is not clear. For example, myasthenia gravis, chronic active hepatitis and diabetes mellitus may occur more frequently in the HLA-B8-homozygous person.[15] In contrast, B27-related disorders probably occur with equal prevalence in the B27 homozygote or heterozygote. As a corollary, the prevalence of B27 homozygosity among a group of spondylitics is comparable to that among a control population. It has been suggested that homozygosity for B27 results in more severe disease,[35] however, such reports may reflect publication bias rather than actual fact. The consensus is that no definite effects based on gene dosage have been shown in rheumatologic disorders.

The Risk to HLA-B27-Positive Persons

In 1975, we showed that about 20 percent of HLA-B27-positive blood donors had symptomatic sacroiliitis regardless of gender.[36] At the same time, findings from a study of B27-positive male blood donors showed a comparable prevalence of *spondylitic stigmata*.[37] Other studies[38-40] as well as our experience with the Pima Indians[32] have provided similar figures. If in 20 percent of HLA-B27-positive persons symptomatic sacroiliitis (ankylosing spondylitis) develops without obvious environmental insult, then about 1 percent of all whites will have the disease. This figure is much greater than the often quoted ratios of 1:1,000 for males and 1:10,000 for females. It is clear that in most persons with ankylosing spondylitis the condition is unrecognized. Certainly, many persons with this disease are misdiagnosed, and therefore undergo inappropriate testing procedures (for example, myelograms) and treatment (such as bedrest or laminectomies). Radiologists and physicians must appreciate that ankylosing spondylitis may be diagnosed in the presence of minimal sacroiliitis. Total loss of the sacroiliac joints or spinal involvement is unnecessary for a diagnosis to be reached. It is hoped that with increased awareness of and interest in the HLA-B27-related disorders by physicians, the misdiagnosed and mismanaged spondylitic condition will soon be a phenomenon of the past.

As mentioned, many older texts suggested that ankylosing spondylitis occurs ten times more frequently in men than women. This claim results in a delay and reluctance to diagnose the condition in women.[41] Moreover, women with ankylosing spondylitis tend to have more peripheral joint involvement and less severe spinal disease than men.[42] Therefore, this spondylitic condition

in women was often diagnosed as seronegative rheumatoid arthritis. A more accurate ratio based on gender is two or three males to one female. What is the explanation for this sex difference? Why do women have more peripheral joint involvement? These and other questions remain unanswered. As suggested, the difference may be explained in part by lack of clinical sophistication, but other factors are certainly relevant.

A reactive arthropathy or typical triad of the Reiter syndrome (arthropathy, inflammatory eye disease and urethritis) following nonspecific urethritis or a definitive infective episode (such as yersiniosis, salmonellosis or shigellosis) develops in about 20 percent of HLA-B27-positive persons. Whether the same 20 percent of HLA-B27-positive persons are at risk for ankylosing spondylitis occurring following an unknown event or the Reiter syndrome developing following a specific infection remains unknown.

Of interest, according to J. P. Gofton, MD, (unpublished observation, 1978) and P. H. Bennett, MD, (unpublished observation, 1978) ankylosing spondylitis is apt to develop in certain populations such as the Pima and Haida Indians and North African Arabs (B. Amor, MD, unpublished data, 1978), while Reiter syndrome is rarely seen in these ethnic groups. Because the infective precipitating agents are mostly ubiquitous, it may be that American Indians and Arabs are *immune* to the relevant infectious agent that has been present since childhood.

Etiology of Ankylosing Spondylitis

HLA Data

In trying to identify environmental factors that may trigger ankylosing spondylitis, we have discovered the following clues: (1) At least 90 percent of white patients with primary disease (that is, in the absence of psoriatic arthropathy, the Reiter syndrome or inflammatory bowel disease) carry the antigen HLA-B27.[24,25] (2) Although sacroiliitis may occur with equal prevalence in both sexes, the disease tends to be more severe in males. (3) There appears to be no association between ankylosing spondylitis and the HLA-D or DR region.[43] This striking finding is in contrast to most other disorders where the primary association is with the D region. (4) A secondary form of spondylitis may develop in patients with post-Shigella (and other infective) arthropathies. (5) The disease is found in populations in most geographic areas, but is more common in those ethnic groups with a higher prevalence of HLA-B27 (6) Nonwhites are less frequently B27 positive than their white counterparts. (7) This disease tends to develop in persons during their early decades.

Results of a recent study from Iceland suggested that ankylosing spondylitis is more likely to develop in persons with both HLA-B27 and the B_FS allele of properdin B factor (alternative complement pathway) than in persons with B27 and the B_FF allele.[44] Because the B_F locus is situated on the D side of the B locus on the sixth chromosome, the disease gene, if not HLA-B27 itself, appears to be located between HLA-B and D. However, these findings were not confirmed in an Italian study.[45] Previous investigations have suggested that ankylosing spondylitis is more likely to develop in persons with HLA-A2 and B27 than in HLA-A2-negative persons.[46] It also appears that there is a greater risk that ankylosing spondylitis develops in persons with HLA-A28 and B27 than in A28-negative persons.[47,48] In this instance, the disease gene would be located on the HLA-A side of the B locus. The situation is further confused by two conflicting reports, one incriminating HLA-CW1 and CW2 in the pathogenesis of spondylarthropathies[49] and the other refuting this suggestion.[50] In essence, the debate as to whether HLA-B27, itself, or a nearby disease-specific gene is relevant in the pathogenesis of ankylosing spondylitis continues.

The Single-Gene Theory (B27 Itself)

The hypothesis that HLA-B27 itself is instrumental in the pathogenesis of ankylosing spondylitis (that is, a single-gene effect) has received support for several reasons. There is no HLA-D link in spondylitis,[43] and the very high association between B27 and the disease suggests that B27 itself is of paramount importance. Moreover, certain studies have suggested that even in the absence of HLA-B27, one of the cross-reacting antigens (HLA-B7, B22 or BW42) is present.[51] Because these antigens may appear *similar* to the putative infective agent, the disease may develop regardless of which of the cross-reacting antigens is present. It is postulated that the infective agent, not recognized as foreign by the host, may replicate and cause disease (cross-tolerance) or that the body mistakes the infective agent for self-tissue and destroys both the self-tissue and the

invading offender (molecular mimicry).[52] As an example, acute rheumatic fever may result from molecular mimicry; the host antibodies cross-react with the streptococcal M antigen and cardiac tissue. The fact that B27 is associated with disease in different ethnic groups is an additional argument in favor of the role of B27 itself. This situation contrasts with the finding in thyrotoxicosis. Whites are HLA-B8 positive while Japanese are B5 positive.[53] In this situation, it is postulated that B8 and B5 occur in linkage disequilibrium with the appropriate disease gene in the two ethnic groups, respectively. Finally, the suggestion that Klebsiella cross-reacts with HLA-B27 provides further support for the role of B27 itself.[54,55]

The Disease-Associated Gene Theory (Second Gene)

The alternative theory, stating that B27 is merely a marker for a specific disease-associated gene, has received limited support. In non-B27-related disorders, the D association is usually greater than the B association, suggesting that the disease gene is in the HLA-D region. After extrapolating data from animal studies,[52] investigators have considered that this area may include immune-response genes. This theory is best suited to those disorders that are clearly autoimmune. There is now increasing evidence that ankylosing spondylitis and the Reiter syndrome are not the immunologically silent disorders that they appeared to be.[56] Thus, there may be an HLA-linked immune-response gene related to the pathogenesis of these disorders. Moreover, results of studies have shown that it is more likely that the Reiter syndrome rather than ankylosing spondylitis will develop in persons with HLA-A3-B27.[46] If this is true, it suggests that the haplotype is relevant in disease pathogenesis rather than the specific antigen, B27 itself. Also, varying degrees of association between HLA and disease in different ethnic groups (such as Japanese, Pima Indians, blacks and whites) suggest that HLA-B27 may occur in differing linkage disequilibrium with the specific disease-associated gene. Finally, the fact that ankylosing spondylitis can occur in persons in whom there is an absence of HLA-B27 needs to be explained. In fact, such a condition is rarely found in the absence of one of the cross-reacting antigens or a primary disorder such as psoriatic arthropathy or the Reiter syndrome.

Findings from some family studies have shown that HLA-B27-positive persons who are healthy can be related to HLA-B27-negative patients with ankylosing spondylitis. This supports the second theory; the inference being that a cross-over has occurred between B27 and the disease gene itself. Finally, B27 is associated with different diseases, and therefore may be a marker for different disease genes (for example, ankylosing spondylitis or the Reiter syndrome).

In summary, different mechanisms are probably required to explain these various disease associations.[52]

Non-HLA Gene Contributions and Genetic-System Interactions

The situation is complicated still further by the fact that non-HLA-related genes may also be involved in the pathogenesis of rheumatic diseases. For example, HLA-DW4 (on chromosome 6) and the MZ phenotype of alpha-1 antitrypsin (on a different chromosome) may interact in the pathogenesis of rheumatoid arthritis and fibrosing alveolitis.[57] Similarly, the MZ phenotype and HLA-B27 are associated more frequently than would be expected by chance alone in ankylosing spondylitis and uveitis.[58] No doubt, other interactions between different genetic systems will be clarified in the future.

The Search for Infective Agents

The fact that monozygotic twins may be discordant for ankylosing spondylitis[59] is proof of the necessity for environmental trigger factor(s). A report incriminating Klebsiella in the pathogenesis of ankylosing spondylitis[54] has not received bacteriologic support from other investigators.[60,61]

However, recent evidence[57] suggesting that Klebsiella antigens do cross-react with a gene product closely associated with HLA-B27 or with Klebsiella-associated B27 antigen, adds credence to the earlier observation.[54] Because the Reiter syndrome may be caused by several infective agents (for example, Shigella and Salmonella) it seems possible that more than one organism may precipitate ankylosing spondylitis in a susceptible host. Moreover, because ankylosing spondylitis occurs with an appreciable prevalence (20 percent of all B27 subjects), regardless of geographic location, it appears that the infective agent is ubiquitous, or that many different organisms or toxins are involved.

The Reiter Syndrome: Genetics Versus Environment

The Reiter syndrome is provocative for rheumatologists because a clearly defined infection (for example, Shigella) in the presence of a specific genetic background (HLA-B27) leads to a chronic rheumatic disease (the Reiter syndrome). The recognized infective events in the pathogenesis of Reiter disease include both venereal and enteric infections. It is important to note that urethritis, per se, may be either the precipitating infective event or a noninfective manifestation of a primary dysenteric (infective) bowel process.[62]

Venereally Acquired (Endemic) Reiter Syndrome

Nonspecific urethritis, as a precipitating event, may be caused by Chlamydia[63] in about 30 percent to 40 percent of cases, by Ureaplasma urealyticum (formerly called T strains of mycoplasma) in some patients and by unrecognized infective agents in the remaining patients.[64] In between 1 percent and 3 percent of persons who present with nonspecific urethritis, a partial form, the full triad or more features of the Reiter syndrome will develop.[65,66] Extrapolating from incidence figures of Csonka,[65] Laird[66] and other investigators, and knowing the prevalence of HLA-B27 in these communities, it appears that nonspecific urethritis will progress to Reiter disease in about 20 percent of HLA-B27-positive patients. The similarity between this 20 percent figure and that mentioned for ankylosing spondylitis is striking.

It remains unclear whether Ureaplasma urealyticum causes the Reiter syndrome, but Chlamydia has been incriminated as a precipitating agent in studies carried out in London[63] and California.[67] The London investigators showed that 36 percent of patients with nonspecific urethritis had positive cultures for Chlamydia as did 43 percent of persons with "sexually acquired reactive arthritis." More specifically, 50 percent of the former group had increased titers of IgG antibody to Chlamydia (greater than 1:16) compared with 73 percent of patients with reactive arthropathy. Control figures include 10 percent for rheumatoid arthritis, 23 percent for lupus, 13 percent for ankylosing spondylitis and 10 percent for healthy subjects. The geometric mean titers for the nonspecific urethritis and reactive arthropathy patients were 7.8 and 42.2, respectively. This striking difference was not related to the B27 status of the arthropathy subjects. These findings suggest that there are different host responses to Chlamydia in those persons in whom arthropathies later develop compared with those in whom only nonspecific urethritis will develop.[68] The responsible agent for the development of venereally acquired Reiter syndrome in those patients without evidence of chlamydial infection remains unclear. Likewise, what determines whether patients will have a limited form of the Reiter syndrome, the full triad or more features also remains uncertain. The effect of HLA-B27 is discussed below.

Postdysenteric (Epidemic) Reiter Syndrome

Shigella, Salmonella and Yersinia infections are associated with the Reiter syndrome in 1 percent to 4 percent of patients. Again, the risk for an HLA-B27-positive person in whom one of these enteric infections develops appears to be in the range of 20 percent to 30 percent. These figures are derived from our own follow-up study[69] of post-Shigella Reiter syndrome and Scandinavian experience with Salmonella typhimurium[70,71] and Yersinia.[72,73]

In an attempt to carry out prospective studies we evaluated Shigella flexneri types 1b and 2a and Shigella sonnei epidemics in the United States. In a controlled study[74] we confirmed that S. flexneri type 2a was arthritogenic,[75] that S. flexneri type 1b caused Reiter disease and that S. sonnei was not associated with the Reiter syndrome.[74] Of interest, again, in about 20 percent of B27-positive subjects Reiter disease developed after contact with the arthritogenic agent.

In addition to Shigella, Yersinia and Salmonella, other infective agents may cause a similar disease. For example, reports[76,77] have incriminated Campylobacter fetus jejuni in the pathogenesis of the Reiter syndrome.

The Sex Ratio of the Reiter Syndrome

In contrast to the apparent sex ratio of 10:1 in favor of male patients with the postnonspecific urethritis form of the disease, the sex ratio of post-Yersinia, Salmonella and Shigella arthritis is equal. Because the Reiter syndrome is difficult to recognize in women, the 10:1 ratio may be exaggerated. Moreover, it is likely that nonspecific urethritis, itself, occurs more frequently in males than females (perhaps 5:1), so it may be that the initial infection rather than the resulting rheumatic syndrome is sex related. In our own experi-

ence with the epidemic form of the disease, the syndrome developed in more women than men.[74]

In conjunction with membrane biologists, we are carrying out studies to analyze the nature of arthritogenic and nonarthritogenic Shigella strains in an attempt to define the specific arthritogenic component in the bacterial cell wall.

The Effect of HLA Status on Disease Severity

The severity of ankylosing spondylitis in HLA-B27-positive and HLA-B27-negative patients appears to be comparable. In contrast, results of previous studies have suggested that Yersinia arthropathy,[73] endemic Reiter syndrome[78] and post-Shigella disease[69] are more severe in HLA-B27-positive patients than in their negative counterparts. However, in our own experience of 131 consecutive cases of the Reiter syndrome (four fifths of the patients had the nonspecific urethritis form of the disease), there appeared to be no difference between the HLA-B27-positive and HLA-B27-negative subjects,[79] apart from an increased prevalence of eye and spinal disease in HLA-B27-positive subjects. About 80 percent of our patients were B27 positive. The chronicity of the Reiter syndrome is also apparent in this study. At follow-up at a mean of 5.6 years, 85 percent of consecutive patients had active disease ranging from minimal symptoms to major disability. This attests to the importance of the Reiter syndrome as a chronic rheumatic disorder.

Psoriatic Arthropathy and HLA

We have recently described a pair of monozygotic twins discordant for psoriatic arthropathy.[80] The twins are now 67 years old and the affected twin has had severe skin disease and arthropathy for almost 50 years. Clearly, an environmental factor must have precipitated the disease in the affected brother. Psoriasis itself appears to have multiple associated genes[81] and a gene-dependent, age-related onset. Patients less than 20 years of age are more likely to have BW17 while older patients have BW16. The closest association between psoriasis and HLA incriminates a CW specificity (CW6).[12] HLA-BW38 occurs more frequently in patients with psoriatic arthropathy than in a control psoriatic population.[82] The relationship between the skin disease, peripheral arthropathy and spondylitic manifestation remains unclear.

Other Infections and Rheumatic Disease

In view of the recognized defects in host-defense mechanisms that may predispose to infection,[83] it is surprising that there are no further associations between specific infective arthropathies and HLA. Poststreptococcal rheumatic fever is not related to HLA-B27, and its possible associations with other HLA antigens are controversial. One recent study[84] suggested a modest increase in BW35 and decrease in B5. This latter observation is of interest because persons with HLA-B5 are more likely to have increased *in vitro* responses to streptococcal antigens.[85]

The arthropathy following natural rubella or vaccination is not B27 associated, and no other specific deviations have been described.[86] Four clinically distinct rheumatologic syndromes are associated with hepatitis B virus.[87] These include a transient, symmetrical polyarthritis occurring as a prodrome of icteric or anicteric acute hepatitis B, a similar arthropathy seen during the course of chronic active hepatitis, a polyarteritis occurring in patients with HBsAg, and the recently described association between hepatitis B and *essential* mixed cryoglobulinemia. To date, no genetic studies of these disorders in large numbers of persons have been carried out. However, it is likely that genetically determined differences in host response predispose to different clinical syndromes. Inman recently reviewed the effects of gender and response to infection.[88] The difference in how male and female patients respond to the hepatitis B antigen may be related to the different rheumatic syndromes that result from hepatitis B infection.

Polymyalgia Rheumatica and Temporal Arteritis

Increases in HLA-B5 and BW38 have been reported in patients with polymyalgia rheumatica, particularly in those subjects who also had temporal arteritis, but not in those with temporal arteritis alone. If confirmed, it would appear that polymyalgia rheumatica and temporal arteritis are distinct entities or that polymyalgia rheumatica is more likely to develop in patients with temporal arteritis and B5 or BW38.[89]

Vertebral Ankylosing Hyperostosis and Osteitis Condensans Ilii

At one time it was considered that vertebral hyperostosis was associated with HLA-B27.[90] This led to the supposition that B27 might be associated with a propensity to develop new bone. Further studies, however, have not confirmed this association.[91] That osteitis condensans

ilii is a condition unrelated to ankylosing spondylitis has been confirmed by the absence of B27.[92]

Behcet Disease

There is a suggestion that Behcet disease may be infective in origin.[93] In patients in Japan, an association between this disease and HLA-B5 has been noted.[94] In contrast, no such association was found in patients in Great Britain in whom there is a weak link between Behcet disease and B27.[95]

The Sjögren Syndrome

HLA-B8 and DW3 are associated with the Sjögren syndrome in patients with primary disease. However, no such link has been noted in patients with the Sjögren syndrome related to rheumatoid arthritis, suggesting that the latter may be a separate disorder.[96]

Renal Disease and Rheumatology

The Goodpasture syndrome is associated with HLA-DRW2.[97] This specificity is in linkage disequilibrium with B7. Multiple sclerosis is similarly associated. Of interest, both conditions tend to have periods of relapse and remission and may be associated with infections or other environmental events. Finally, IgA glomerulonephritis (Berger disease) does not have this or any other HLA association.[98]

Conclusion

Rheumatologic diseases result from a complex interaction between host and environment, and physicians will be successful in treating these disorders only when they learn how to modify one, the other or both. We are beginning to recognize certain genetic contributions; it is hoped that this will lead to increased understanding of the host response and the nature of the causes involved. If progress in research continues at its present rate, our initial optimism will not be ill founded.

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